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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/519,959	03/07/00	CARRASCO N	96700/488

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EXAMINER	
RAWLINGS,S	

ART UNIT	PAPER NUMBER
1642	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/519,959	Applicant(s) CARRASCO ET AL.	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *12-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims *1-28* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. The election with traverse of Group I in Paper No. 8 filed on March 16, 2001 is acknowledged and has been entered. The election of species also in Paper No. 8 is acknowledged and has been entered.

2. Claims 1-28 are pending in the application. Claims 12-28 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

3. Claims 1-11 are currently under prosecution.

Election/Restrictions

4. Applicant's election with traverse of Group I (claims 1-6) in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the search of inventions in Groups I-III is coextensive and therefore is not a serious burden. This is found persuasive and accordingly Groups II and III are rejoined with Group I. As such, the elected Group to be examined now consists of claims 1-11.

With regard to the elected group, the requirement for an election of species is hereby withdrawn, because the search of both species is coextensive and therefore not a serious burden.

With regard to the remaining Group I (now rejoined with Groups II and III) and Groups IV-IX, because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the requirement is still deemed proper and is therefore made FINAL.

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Inventor Irene L. Wapnir did not date the declaration.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-11 are indefinite because there is no positive correlation step which clearly relates back to the preamble of claim 1. Amending claim 1 to recite, for example, the phrase "whereby the subject is diagnosed with breast cancer" in the last line can obviate this rejection.

Claim 3 is vague and indefinite because the claim recites the term "reactive" in line 2. The use of the term "reactive" renders the claim indefinite because it cannot be ascertained how the agent is required to react with mgNIS (e.g., it is unclear whether the agent is required to bind mgNIS, phoshorylate mgNIS, glycosylate mgNIS, cleave mgNIS, derivatize mgNIS, etc.). According to the specification, " 'reactive' means the agent has affinity for, binds to, or is directed against mgNIS" (page 9, lines 19-20). However, the use of the term still renders the claim vague and indefinite for the reason already given. For example, a protease can be said to have affinity for mgNIS, to bind mgNIS, and to be directed against mgNIS. Therefore, one of ordinary skill in the art is not reasonably apprised of the metes and bounds of the invention.

Claim 5 and 6 are also indefinite because the claims depend from claim 3, which recites the term "reactive" in line 2. The recitation of the term "reactive" in claim 3

renders claim 5 indefinite because, while it is reasonably apparent that with regard to an antibody, the term "reactive" means to bind to mgNIS, it is unclear whether the antibody must bind specifically or otherwise. Certainly, an antibody can bind non-specifically or non-selectively, which would, of course, limit the usefulness of the invention. Therefore, one of ordinary skill in the art is not reasonably apprised of the metes and bounds of the invention. Amending claim 3 to recite, for example, the phrase "wherein the expression of mgNIS is detected using an agent that specifically and selectively binds mgNIS" can obviate this rejection.

Claims 7-9 are also indefinite because claim 7 recites the term "hybridizes". The use of the term "hybridizes" renders the claim indefinite because it cannot be ascertained whether the probe must hybridize specifically and selectively to the nucleic acid encoding mgNIS. Certainly, it is well known in the art that hybridization conditions, which are chosen at the discretion of the investigator, are highly variable and can provide very different results. Therefore, one of ordinary skill in the art is not reasonably apprised of the metes and bounds of the invention. Amending claim 7 to recite, for example, the phrase "wherein the expression of mgNIS is detected using at least one nucleic acid probe that specifically and selectively hybridizes under stringent conditions to the nucleic acid encoding mgNIS" may obviate this rejection. Still better, amending claim 7 to recite the phrase "wherein the expression of mgNIS is detected and quantified by Northern blot analysis of RNA samples prepared from the breast tissue of the subject" can obviate this rejection. However, Applicant is cautioned against the addition of new matter to the claims.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 2, 10, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Cancroft, et al (*Radiology* **106**: 441-444, 1973; Form PTO-1449, citation 1), as evidenced by Socolow, et al (*Endocrinology* **80**: 337-344, 1967), Tazebay, et al (*Nature Medicine* **6**: 871-878, 2000), and Spitzweg, et al (*Journal of Clinical Endocrinology* **83**: 1746-1751, 1998; Form PTO-1449, citation 25).

The claims are drawn to a method of diagnosing breast cancer in a subject, said method comprising detecting the expression of mammary gland sodium/iodide symporter in the breast tissue of the subject (claim 1), wherein the expression of the symporter is detected *in vitro* or *in vivo* (claim 2) using a detectable agent that is selectively taken up by the symporter (claim 10) wherein the agent is radioiodide or ^{99m}Tc-pertechnetate (claim 11).

Socolow, et al provide evidence that ^{99m}Tc-pertechnetate is selectively taken up by the thyroid gland (abstract) by a mechanism that resembles the mechanism by which radioiodide is taken up by the cells. Also, see Tazebay, et al, which indicates that ^{99m}Tc-pertechnetate is selectively taken up by cells that express NIS (page 872, column 2). Spitzweg, et al provide evidence that the ability of thyroid tissue to selectively concentrate radioiodide (and ^{99m}Tc-pertechnetate) is dependent upon the activity of NIS, which is commonly expressed in breast tissue also.

Cancroft, et al teach a method for diagnosing breast cancer in a subject, said method comprising scintigraphic imaging of tumor masses by administering ^{99m}Tc-pertechnetate to the subject (abstract). Cancroft, et al disclose that "in patient A.Y., a lesion of the left breast diagnosed as malignant on mammography was readily observed on scintigraphy" (page 443, column 1). While Cancroft, et at teach that the mechanism of ^{99m}Tc-pertechnetate concentration in malignant breast masses is not clear, it is an inherent feature of ^{99m}Tc-pertechnetate to concentrate in the malignant breast masses by a mechanism involving its selective uptake by NIS, as evidenced by Socolow, et al and Spitzweg, et al. In the method of Cancroft, et al, the level of ^{99m}Tc-pertechnetate taken up by a cancer cells reflects the level of expression in the cells of mgNIS, which is responsible for the uptake of ^{99m}Tc-pertechnetate. Therefore, the level of radioactivity detected in the cells is a measure of the level of mgNIS expression in the subject's

breast cancer cells; thus, the diagnostic method of Cancroft, et al intrinsically detects the expression of mgNIS in the cancer cells

Moreover, the claims are directed to a method for diagnosing breast cancer in a subject. The selective uptake of ^{99m}Tc-pertechnetate by mgNIS facilitates the diagnosis of breast cancer by scintigraphic imaging, which detects the presence and localizes malignant breast cancer cells that have concentrated the detectable agent. The method of the prior art comprises the same method steps as claimed in the instant invention, that is, administering ^{99m}Tc-pertechnetate to a subject that is to be diagnosed with breast cancer. Thus, the claimed method is anticipated because the prior art method will inherently lead to conferring a diagnosis of breast cancer in the subject. See *Ex parte Novitski* 26 USPQ 1389 (BPAI 1993).

All the limitations of the claims are met.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cancroft, et al (*Radiology* **106**: 441-444, 1973; Form PTO-1449, citation 1) in view of Eskin, et al (*Obstetrics and Gynecology* **44**: 398-402, 1974; Form PTO-1449, citation 9), Kilbane, et al (Spitzweg, et al (*Journal of Clinical Endocrinology* **83**: 1746-1751, 1998; Form PTO-1449, citation 25) and Jhiang, et al (*Endocrinology* **139**: 4416-4419, 1998; Form PTO-1449, citation 11).

The subject matter of claims 1, 2, 10, and 11 is set forth in the 35 USC § 102(b) rejection above. Claims 3-6 are drawn to a method for diagnosing breast cancer in a subject, as in claim 1, wherein the expression of mgNIS is detected using a detectably labeled reagent, such as an antibody. Claims 7-9 are drawn to a method for diagnosing

breast cancer in a subject, as in claim 1, wherein the expression of mgNIS is detected using a detectably labeled nucleic acid probe, which hybridizes to the nucleic acid molecule encoding mgNIS.

Cancroft, et al teach that which is set forth in the 35 USC § 102(b) rejection above. However, Cancroft, et al do not expressly disclose that the expression of mgNIS can also be measured using radioiodide, which is a detectable agent that is selectviely taken up by mgNIS. Furthermore, Cancroft, et al do not expressly disclose that the expression of mgNIS can also be measured using either a detectably labeled anti-mgNIS antibody (e.g., a Western blot analysis) or a detectably labeled nucleic acid probe that hybridizes to the mRNA molecule that encodes mgNIS (e.g., a Northern blot analysis).

Eskin, et al teach that "pilot studies show that ^{131}I concentration in biopsied human breast tissues with carcinoma or dysplasia is higher than in histologically normal tissues from the same patient" (abstract). Eskin, et al conclude that the use of the diagnostic technique has several advantages (page 402, column 1), because of the fact that breast cancer takes up a greater amount of radioiodide.

Spitzweg, et al teach a method for detecting the expression of human NIS in tissue samples acquired from a subject (abstract) by Northern blot analysis, which utilizes a nucleic acid probe that specifically hybridizes to mRNA encoding human NIS (page 1747, column 1). Spitzweg, et al also teach that the ability of thyroid tissue to selectively concentrate radioiodide is dependent upon the activity of NIS, which is commonly expressed in breast tissue also. Specifically, Spitzweg, et al teach that "the nucleotide sequences of hNIS cDNA derived from parotid gland, mammary gland, and gastric mucosa revealed **full identity with the recently published human thyroid-derived NIS cDNA sequence**" (emphasis added) (abstract). Spitzweg, et al conclude, "our detection of significant quantities of hNIS [human sodium/iodide symporter] gene expression in thyroid gland, salivary glands, thymus, pituitary gland, pancreas, testis, mammary gland, and gastric mucosa, and lower degrees of NIS gene expression in prostate, ovary, adrenal gland, lung, heart, and nasopharyngeal mucosa suggests that

iodide transport in some of these tissues may be **a specific prop rty conf rr d by the expression of NIS**" (emphasis added) (page 1750, column 1).

Jhiang, et al teach the immunohistochemical analysis of human sodium/iodide symporter (NIS) expression in tissue samples acquired from a subject (abstract). More specifically, Jhiang, et al teach that an antibody that is detectably labeled, which specifically binds to human NIS, can be used in Western blot analysis of membrane fractions from cells isolated from a subject (page 4417, column 1). Furthermore, Jhiang, et al teach that the antibody can also be used to stain frozen tissue sections and paraffin-embedded tissue sections acquired by patient biopsy (page 4417, column 1-2). Clearly, both of the methods can be used to detect the expression of human NIS in the cells of a subject.

The human NIS to which the prior art antibody binds appears to be the same as mgNIS of the instant claims, absent a showing of unobvious differences. By the same token, it appears that the prior art nucleic acid probe hybridizes to the same nucleic acid molecule encoding mgNIS of the instant claims, absent a showing of unobvious differences. The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed antibodies or probes are functionally different than those taught by the prior art and to establish patentable differences. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Board of Patent Appeals and Interferences).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute radioiodide, such as ^{131}I for ^{99m}Tc-pertechnetate in the method of Cancroft, et al to diagnose breast cancer in a subject, because Spitzweg, teaches that radioiodide is also selectively taken up by cells that express NIS, such as mammary gland. One of ordinary skill in the art at the time the invention was made would have been motivated to substitute ^{131}I for ^{99m}Tc-pertechnetate in the method of Cancroft, et al because, since ^{131}I is a β-particle emitter

that can kill cancer cells, the treatment will benefit the patient by having a therapeutic effect, in addition to providing the differential diagnosis.

Furthermore, in view of the teachings of Spitzweg, et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to identify the presence of breast tissue that expresses relatively higher levels of mgNIS by either the method of Jhiang, et al or Spitzweg, et al, because Cancroft, et al teaches that a method that detects the differential concentration of ^{99m}Tc-pertechnetate in breast cancer cells is diagnostic of breast cancer and because Eskin, et al teaches that breast cancer cells concentrate higher amounts of radioiodide than histologically normal breast tissue. One of ordinary skill in the art at the time the invention was made would have been motivated to combine the methods of either Jhiang, et al or Spitzweg, et al with the diagnostic method of Cancroft, et al to confirm the diagnosis of breast cancer in the subject by an analysis of the level of mgNIS expression in biopsied tissue, because using a second reliable diagnostic method can prevent a misdiagnosis. It also would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the antibody of Jhiang, et al in a modification of the diagnostic method of Cancroft, et al, because the detectably labeled anti-mgNIS antibody also can be used to specifically and selectively target cancer cells that express mgNIS. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to modify the method of Cancroft, et al by using the antibody of Jhiang, et al to confirm the diagnosis of breast cancer in a subject using a second reliable method, in order to avoid a misdiagnosis.

Conclusion

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Art Unit 1642

slr
April 20, 2001

DONNA WORTMAN
PRIMARY EXAMINER